Remarks/Arguments

The foregoing amendments in the claims are of formal nature, and do not add new matter.

Claims 39-46, 49-51 are pending in this application and are rejected on various grounds. Claims 1-38 and 47-48 were previously canceled without prejudice or disclaimer. Although the Examiner withdrew some rejections; the rejections to claims under 35 USC § 101 and 35 USC § 112, first paragraph are maintained; Applicants respectfully traverse these rejections.

Claim Rejections – 35 USC § 101/ 112, first paragraph

Claims 39-46 and 49-51 are rejected under 35 USC § 101/112, first paragraph, since allegedly, "the claimed invention is not supported by either a specific or substantial asserted utility or a well established utility."

While the Examiner acknowledges that "real-time PCR" is a reliable means of determining gene copy number in cells or tissues, the Examiner asserts that utility for even the nucleic acid is not resolved by the Goddard declaration because of aneuploidy. The Examiner also asserts that "even if the nucleic acid had utility as a lung and colon tumor marker, the encoded polypeptide would not have utility because it is not known what the protein does or if the level of PRO339 protein in tumors corresponds to nucleic acid transcript level(s)." From this, the Examiner concludes that the PRO339 polypeptide lacks specific or substantial utility.

Applicants respectfully disagree.

Claims 39-43 have been amended for clarity to recite "wherein the nucleic acid encoding said polypeptide is amplified in lung tumor". Regarding the Examiner's lack of utility rejection based on a lack of explanation for aneuploidy, Applicants have enclosed a Declaration by Avi Ashkenazi, Ph.D., an expert in the field of cancer biology and an inventor of the present application. As Dr. Ashkenazi explains,

> An increase in gene copy number can result not only from intrachromosomal changes but also from chromosomal aneuploidy. It is important to understand that detection of gene amplification can be used for cancer diagnosis even if the determination includes measurement of chromosomal aneuploidy. Indeed, as long as a significant difference relative to normal tissue is detected, it is irrelevant if

the signal originates from an increase in the number of gene copies per chromosome and/or an abnormal number of chromosomes.

Further, as discussed below, Applicants submit that the Examiner has not been established a *prima facie* case for lack of utility.

Evidentiary Standard

An Applicant's assertion of utility creates a presumption of utility that will be sufficient to satisfy the utility requirement of 35 U.S.C. § 101, "unless there is a reason for one skilled in the art to question the objective truth of the statement of utility or its scope." *In re* Langer, 503 F.2d 1380,1391, 183 USPQ 288, 297 (CCPA 1974). See, also *In re* Jolles, 628 F.2d 1322, 206 USPQ 885 (CCPA 1980); *In re* Irons, 340 F.2d 974, 144 USPQ 351 (1965); *In re Sichert*, 566 F.2d 1154, 1159, 196 USPQ 209, 212-13 (CCPA 1977).

Compliance with 35 U.S.C. § 101 is a question of fact. Raytheon v. Roper, 724 F.2d 951, 956, 220 USPQ 592, 596 (Fed. Cir. 1983) cert. denied, 469 US 835 (1984). The evidentiary standard to be used throughout *ex parte* examination in setting forth a rejection is a preponderance of the totality of the evidence under consideration. In re Oetiker, 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992) Thus, to overcome the presumption of truth that an assertion of utility by the applicant enjoys, the Examiner must establish that it is more likely than not that one of ordinary skill in the art would doubt the truth of the statement of utility. Only after the Examiner made a proper *prima facie* showing of lack of utility, shifts the burden of rebuttal to the applicant. The issue will then be decided on the totality of evidence.

A prima facie case of lack of utility has not been established

The Examiner bases the conclusion of lack of utility/ enablement on a quote from Pennica *et al.*, submitted as Exhibit D of the Goddard Declaration filed with Applicants' response to the prior Office Action. According to the quoted statement, WISP-1 gene amplification in human colon tumors showed a correlation between DNA amplification and over-expression, whereas overexpression of WISP-3 RNA was seen in the absence of DNA amplification. In contrast,

WISP-2 DNA was amplified in colon tumors, but its mRNA expression was significantly reduced in the majority of tumors compared with expression in normal colonic mucosa from the same patient. From this, the Examiner correctly concludes that increased copy number does not *necessarily* result in increased protein expression. The standard, however, is not absolute certainty. The fact that in the case of a specific class of closely related molecules there seemed to be no correlation with gene amplification and the level of mRNA/protein expression, does not establish that it is more likely than not, in general, that such correlation does not exist. The Examiner has not shown whether the lack or correlation observed for the family of WISP polypeptides is typical, or is merely a discrepancy, an exception to the rule of correlation. Indeed, the working hypothesis among those skilled in the art is that, if a gene is amplified in cancer, the encoded protein is likely to be expressed at an elevated level.

Even if a prima facie case of lack of utility had been established, it should be withdrawn on consideration of the totality of evidence

Even if one assumes arguendo that it is more likely than not that there is no correlation between gene amplification and increased mRNA/protein expression, a polypeptide encoded by a gene that is amplified in cancer would still have a specific and substantial utility. Applicants once again rely on the Dr. Avi Ashkenazi's declaration which explains,

> even when amplification of a cancer marker gene does not result in significant over-expression of the corresponding gene product, this very absence of gene product over-expression still provides significant information for cancer diagnosis and treatment. Thus, if over-expression of the gene product does not parallel gene amplification in certain tumor types but does so in others, then parallel monitoring of gene amplification and gene product over-expression enables more accurate tumor classification and hence better determination of suitable therapy. In addition, absence of over-expression is crucial information for the practicing clinician. If a gene is amplified but the corresponding gene product is not over-expressed, the clinician accordingly will decide not to treat a patient with agents that target that gene product.

Thus, Applicants have demonstrated utility for the PRO339 polypeptide. Further, based on this utility and the disclosure in the specification, one skilled in the art would know how to use the claimed polypeptides at the time of filing.

Accordingly, the present 101/112, first paragraph rejections should be withdrawn.

Claim Rejections - 35 USC § 102 and 103

Claims 39-45 and 49 remain rejected under 35 USC § 102(b) as being anticipated by GenBank Accession No. AB037823 (dated March 14, 2000). Claims 50 and 51 are rejected under 35 USC § 103(a) as allegedly obvious in view of Nilsson et al. (Curr. Opin. Struct. Biol. 192, 2:569-575). In addition, claims 46 and 48 were rejected under 35 USC § 103(a) as allegedly obvious over GenBank Accession No. BAA92640 and "Applicants' Admission on p.34, lines 5-6 and Fleming et al. (Dev., 124:2873-81 (1997)).

The effective date of the primary reference (GenBank Accession No. BAA92640) is March 14, 2000. The gene amplification data, which supports the utility of the presently claimed polypeptides were first disclosed in **PCT/US00/03565 filed on February 11, 2000**, the priority of which is claimed in the present application. Since the present application is entitled to at least the February 11, 2000 priority, GenBank Accession No. BAA92640 is not prior art. Accordingly, the present rejections should be withdrawn.

Hence, Applicants respectfully request withdrawal of this rejection.

The present application is believed to be in *prima facie* condition for allowance, and an early action to that effect is respectfully solicited.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 08-1641 (Attorney Docket No.: 39780-1618P2C50). Please direct any calls in connection with this application to the undersigned at the number provided below.

Respectfully submitted,

Date: October 14, 2003

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